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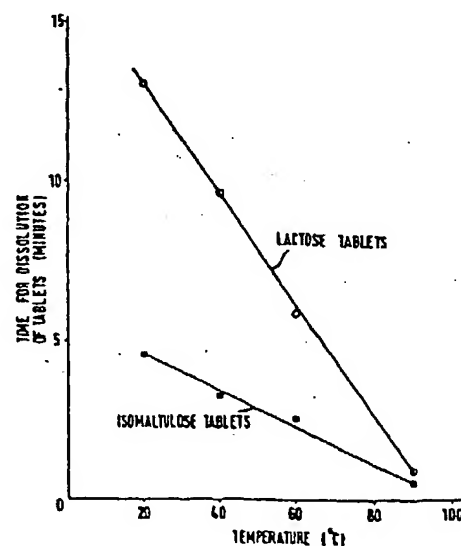
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54 Tablets containing isomaltulose, their use and a method of producing them.

57 Isomaltulose is of use as a diluent in tablets.



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"TABLETS" **TITLE MODIFIED**  
see front page

The present invention relates to tablets, and in particular it relates to tablets which include a diluent material.

5       Tablets are conventionally made by moulding or compressing ingredients, and form a suitable means for delivery of an active ingredient, pharmaceutical or otherwise. There is also a large market for sweets in the form of tablets containing flavouring material as active ingredients.

10       In order to produce tablets, it is necessary to have a free-flowing material which has good self-binding properties and which will not stick to the moulding or compression equipment. Such properties are obtained by using diluents and one or more additives, for example binders and/or lubricants, and by controlled granulation of the ingredients. Some diluents of themselves possess binding  
15       and/or lubricating properties, but normally will require careful granulation.

20       Lactose is a commonly used diluent, having an acceptable taste. However, lactose alone has little adhesive property and normally requires the use of a binder. Moreover, moist granulation is usually needed, involving wetting of the ingredients to give a

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moist, coherent powder, then sieving, and controlled drying to give granules suitable for preparation of tableting powders.

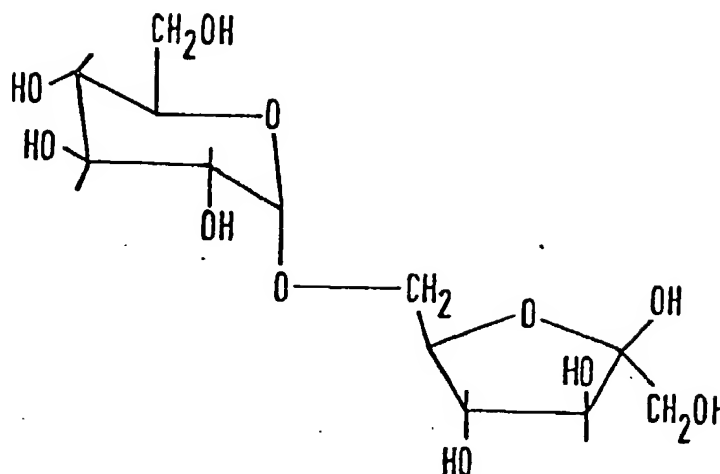
Sucrose, particularly sucrose of small particle size, is also a suitable diluent. Moist granulation is usual, unless one  
5 employs the specially formulated tableting materials such as 'Di-Pac', a blend of maltodextrin and sucrose produced by Amstar Corporation of the USA using a microcrystallization process known as transformation.

Other diluents are in use, for instance, starch, glucose,  
10 mannitol and sorbitol. Each of these materials offers its own advantages for certain uses, but as with lactose and sucrose, binders and/or lubricants along with controlled granulation are normally needed.

We have now found that isomaltulose, a disaccharide with limited previous uses, is especially suitable for use as a diluent  
15 material in tablets. Exceptionally, isomaltulose can give coherent tablets by direct compression with a lubricant, thereby avoiding the need for a binder. More generally, isomaltulose does not seem to require controlled granulation to give a tabletable powder. It is a simple matter to obtain tablets using crystalline isomaltulose  
20 produced by conventional crystallization of isomaltulose solutions.

Isomaltulose is a reducing disaccharide which is sometimes known as palatinose. It has the structure

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and is more systematically known as 6-O-( $\alpha$ -D-glucopyranosyl)-D-fructo-furanose.

Historically, isomaltulose was first mentioned in a 1952 article [J. Amer. Chem. Soc. 74, 3202 (1952)] as a by-product of a fermenting microorganism, Leuconostoc mesenteroides. Subsequent work published in 1956 and 1960 [respectively, J. Amer. Chem. Soc. 78, 2514 (1956) and J. Org. Chem. 25, 1062 (1960)] confirmed the formation of isomaltulose as a by-product of dextran synthesis from sucrose by L. mesenteroides.

The bacterial conversion of sucrose to isomaltulose by P. rubrum was the subject of German Patentschrift No. 1,049,800 in the name of the Suddeutsche Zucker-Aktiengesellschaft. Other bacteria may be used to effect the conversion of sucrose to isomaltulose, and

in their UK Patent Specification No. 1,429,334 (which corresponds to German Patentschrift 2,217,628), the same company mention that Serratia plymuthica is also suitable.

5 The UK Patent Specification No. 1,429,334 is itself directed to the preparation of isomaltitol ( $\alpha$ -D-glucopyranosyl-1,6-sorbitol) from isomaltulose by a catalytic hydrogenation. In practice the hydrogenation gives a mixture that also contains  $\alpha$ -D-glucopyranosyl-1,6-mannitol; this mixture is available as a low calorie sweetener under the trade name 'Palatinit'.

10 More recently, in their European Patent Specification No. 0001099, Bayer Aktiengesellschaft describe a process for continuous fermentation of micro-organisms, for example Protaminobacter rubrum or Serratia plymuthica, with simultaneous conversion of sucrose to isomaltulose. Again the isomaltulose is being prepared for hydro-  
15 genation to give the low calorie sweetener product.

Up until now, the hydrogenation of isomaltulose to a low calorie sweetener appears to have been the principal use for the compound.

In accordance with the present invention we provide a tablet  
20 which contains isomaltulose as the or a diluent material.

Isomaltulose has a particular combination of physical and other properties which we have now discovered make it especially suit-

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able for use as a diluent material in tablets. In particular, isomaltulose has better solubility in water than lactose, does not demand careful, controlled granulation and can be formed into tablets by direct compression with a lubricant.

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Additionally, isomaltulose has a pleasant, not very sweet, reasonably bland taste and can allow other ingredients to exert a flavouring action. Isomaltulose can also contribute bulk, body, mouthfeel and other desired characteristics to tablets for human or animal consumption and to solutions for human or animal consumption prepared from tablets.

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We have determined that isomaltulose has the properties shown in the following Table:

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Isomaltulose Properties.

	solubility at 30°C, H <sub>2</sub> O	46g/100 ml
	viscosity at 25°C, 50%	
	w/v, H <sub>2</sub> O	6 cp
	( $\alpha$ ) <sub>D</sub> <sup>20</sup> at 1% w/v	+ 97°
5	mp	118 - 122°C
	mutatoration (90h at 58°C	
	in 2M HCl)	nil
	reducing power	58 - 62% of that of glucose
	equilibrium relative	
10	humidity (at 80% and 22°C)	
		25 - 32% water
	sweetness (relative to	
	sucrose sweetness at	
	7% w/v in water).	0.37

15            Apart from taking advantage of these determinable properties of isomaltulose, the present invention brings out unexpected beneficial properties of isomaltulose. Thus, tablets employing isomaltulose as diluent often show less tendency to generate fines during handling than are generated during handling of comparable tablets using lactose

20            as diluent. More generally, it was surprising to find that isomaltulose is a suitable replacement for lactose, particularly since other, more common saccharides do not lend themselves to direct tableting. Isomaltulose seems to possess unusually good binding power when formed into tablets.

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Isomaltulose can be used as diluent for various physiologically active ingredients. It can be used not only in pharmaceutical tablets, but also in other tablets containing other kinds of physiologically active ingredients, including flavouring materials. For example, isomaltulose can be used as diluent in sweetener tablets where the active ingredient is a high potency sweetening agent such as saccharin or the sweet protein thaumatin which is extracted from Thaumatococcus daniellii and which is commercially available as Talin (Registered Trade Mark). Such tablets can be used for example to sweeten hot drinks.

In general terms, when proceeding in accordance with the present invention, isomaltulose can be used as a whole or partial replacement of other diluent materials in conventional formulations. Ideally the isomaltulose will be 100% pure, as may be obtained by repeated crystallization of the material prepared by bacterial conversion of sucrose using for example the processes described in German Patentschrift No. 1049800, UK Patent Specification No. 1492334 or European Patent Application No. 0001099. However, we find that acceptable results are obtained using once-crystallized material. Thus, in practice, the isomaltulose can be impure, containing up to 10, 20 or even higher percentage of other saccharides and accompanying matter.

In the specification of the Patent Application entitled "Production of Isomaltulose" which also claims a priority date of 7 November, 1979, there is described a novel process using immobilized



isomaltulose - forming enzyme systems to convert sucrose. The immediate product of this process is an isomaltulose solution also containing sucrose and by-products. Simple crystallization by conventional concentration and cooling procedures can be used to obtain crystals of 90% or higher content of isomaltulose. Such crystals are particularly suited to the manufacture of tablets.

The tablets of the invention can take any of the usual shapes, round, square or otherwise as determined by the equipment used. Suitably the isomaltulose will comprise up to 97% of the tablets of the invention, with 10 to 95% isomaltulose representing a currently preferred range. Apart from active ingredients, which will usually comprise 3 to 90% of the present tablets, and apart from other diluents, such as lactose, the tablets may further contain known tableting additives, for instance to colour the tablets, to aid binding of the ingredients, to give effervescence, or to aid release of the tablets from a tableting machine. The skilled man will be familiar with such additives (eg colouring agents, gum arabic, sodium stearate, starch) and further information is not needed for a sufficient description of the present invention. Tablets of the invention will usually weigh 5 mg to 5g with 50 mg to 500 mg being preferred.

Preparation of the tablets of the invention can be performed using known techniques. In general, a comminuted mix of the isomaltulose and other ingredients is prepared, followed by moulding or compression. Various procedures are available to ensure proper granulation and

intimate and thorough mixing of the ingredients and these procedures can be adopted as appropriate. In some instances it may be necessary to modify the operating conditions so as to ensure that the temperature of the ingredients does not lead to melting of the isomaltulose or to oxidative reaction of the isomaltulose. For instance, with moist  
5 granulation where the ingredients are initially mixed in solution and then dried, it will usually be necessary to dry at from 40 to 95°C.

Unlike lactose and sucrose, isomaltulose crystals produced by ordinary crystallization procedures can give satisfactory tablets  
10 by direct compression after admixture with a lubricant and the intended active ingredient. Thus, in one embodiment of the invention, isomaltulose crystals prepared by crystallization from aqueous solution are dry mixed with a lubricant such as a fatty acid salt and with  
15 the active ingredient to be tableted. Compression of the dry mix is then effected, giving tablets. Overall, this procedure offers advantages over the steps necessary to obtain tablets when using other, common diluents.

Isomaltulose should be acceptable for food and drug use. It has been used as an alternative for isomaltose in in vitro studies  
20 of isomaltose adsorption ("Some Recent Advances in Inborn Errors of Metabolism", Proceedings of Fourth Symposium of the Society for the Study of Inborn Errors of Metabolism held in Dublin, July, 1966, published as a book in 1968 by E and S Livingston, Ed Holt and Coffey,

at page 106 in the paper by Holzen on Disaccharide Intolerances).

As a result of the clinical studies it appears that isomaltulose is readily hydrolyzed by an enzyme complex in the human intestine and that the constituent monosaccharides (fructose and glucose) are adsorbed, metabolized and otherwise behave as fructose and glucose derived from sucrose.

Moreover, preliminary studies indicate that although isomaltulose is metabolized by Streptococcus mutans (the bacterium thought to cause dental caries), little if any dental plaque is formed thereby. There are thus good reasons for believing isomaltulose to be non-cariogenic (that is, a compound which does not induce formation of dental caries).

The present invention is illustrated by the following non-limiting examples. In these Examples, the isomaltulose is crystalline material which is at least 90% pure and which has been prepared by the process of Example 1 in the specification of the said Patent Application entitled "Production of Isomaltulose". Isomaltulose produced by other methods can be used instead.

In Example 1, of the present specification, reference is made to the accompany drawing.

The accompanying drawing is a graph showing the solubility characteristics of tablets embodying the present invention and of comparison tablets.

Example 1 : saccharin tablets

To a mixture of 97 g isomaltulose and 3g gum arabic was added sufficient 20% (w/v) gum arabic solution (12 to 13g) until balls could be formed of the pasty mixture. After thorough mixing, the mixture was passed through a size 16 mesh sieve (1000 microns) and dried at 95°C to give a tablet base composition.

The base composition was re-sieved and 42g of it was intimately mixed with 10 g saccharin, 1 g gum arabic and 3 g sodium stearate, thereby giving a tabletable composition which was formed into about 1,000 tablets using a Manesty hand tableting machine.

Each tablet was well-formed and retained its integrity.

The solubility characteristics of the tablets were investigated in comparison with lactose/saccharin tablets made in exactly the same way except that the isomaltulose was replaced by 96 g of lactose. For various temperatures in the range 20 to 90°C, the time taken for complete dissolution of the tablets was determined under standardized conditions.

The results of the solubility tests were plotted to provide the graphs shown in the accompanying figure : it will be seen that the isomaltulose-based tablets were consistently faster to dissolve than the lactose-based tablets. The faster solubility at the lower temperature is particularly noticeable.

Example 2 : vitamin C tablets

5 90 parts (by weight, all parts being on this basis) of iso-maltulose, were mixed with 10 parts of starch and the mixture granulated using 10% (w/v) starch paste. The resultant granules were dried at about 95°C and screened with a size 16 sieve.

To 58 parts of the granules was added 10 parts of ascorbic acid (vitamin C), 1 part of starch and 1 part of stearic acid, thereby giving a tabletable composition which was formed into tablets. These tablets were of good shape and structure.

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Example 3 : codeine tablets

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A mixture of 160 parts acetylsalicylic acid, 160 parts phenacetin powder and 5 parts codeine phosphate was combined with 8 parts gum arabic, 10 parts starch and 35 parts isomaltulose in order to form granules. After drying at 95°C the granules were mixed with 10 parts starch and 12 parts talc to provide a tabletable composition which was then formed into tablets. Each tablet showed was of consistent shape and did not generate appreciable fines during handling. Dissolution in water was fast.

Example 4

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Further comparisons with lactose were carried out during the preparation of saccharin tablets.

(i) Direct compression

50g isomaltulose, 4g gum arabic, 1g sodium stearate and 13g saccharin were dry mixed, giving a flowable tableting powder. Tablets were formed by direct compression of the powder. No problems with sticking were encountered during compression, and the resultant tablets were hard, cohesive, and yet readily soluble.

In contrast, it was not possible to produce coherent tablets using either 50g lactose or 50g icing sugar in place of the isomaltulose.

(ii) Simplified direct compression

A tableting powder based on isomaltulose was produced in the same way as in Example 4(i) except that the binder (gum arabic) was omitted. Despite the omission of the binder, tablets could still be successfully made by direct compression.

Tablets could not be made using lactose or icing sugar in place of the isomaltulose.

Example 5 : mint sweet

Confectionery in the form of mint-flavoured sweet tablets was made using the following ingredients:

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<u>Ingredient</u>	<u>Amount (parts by weight)</u>
Sucrose	46
Isomaltulose	46
42DE syrup	3
5 Oil of peppermint	3.2
Water	1.2
Magnesium stearate	0.25

The sucrose, isomaltulose, syrup and water were mixed together, extruded in conventional manner and dried at 60°C to give granules.

10 The granules were sieved using a size 30 mesh (0.551 mm) and the oil of peppermint added along with the magnesium stearate. Tabletting in the usual way then gave firm, coherent tablets which dissolved in the mouth, releasing a pleasant peppermint flavour.

## CLAIMS:

1. A tablet which contains isomaltulose as a solid diluent material for one or more active ingredients.
2. A tablet according to claim 1 in which isomaltulose with accompanying impurities is the only diluent material.
3. A tablet according to claim 1 or 2 which contains 10 to 95% of isomaltulose as diluent.
4. A tablet according to any preceding claim which is a pharmaceutical tablet.
5. A tablet according to any of claims 1 to 3 in which the isomaltulose is a diluent for a high potency sweetening agent.
6. A tablet according to any preceding claim, in which the isomaltulose contains no more than 10% impurities.
7. A method of making tablets in which isomaltulose is employed as a solid diluent for one or more active ingredients.
8. A method according to claim 7, in which a dry mix is prepared containing isomaltulose, one or more active



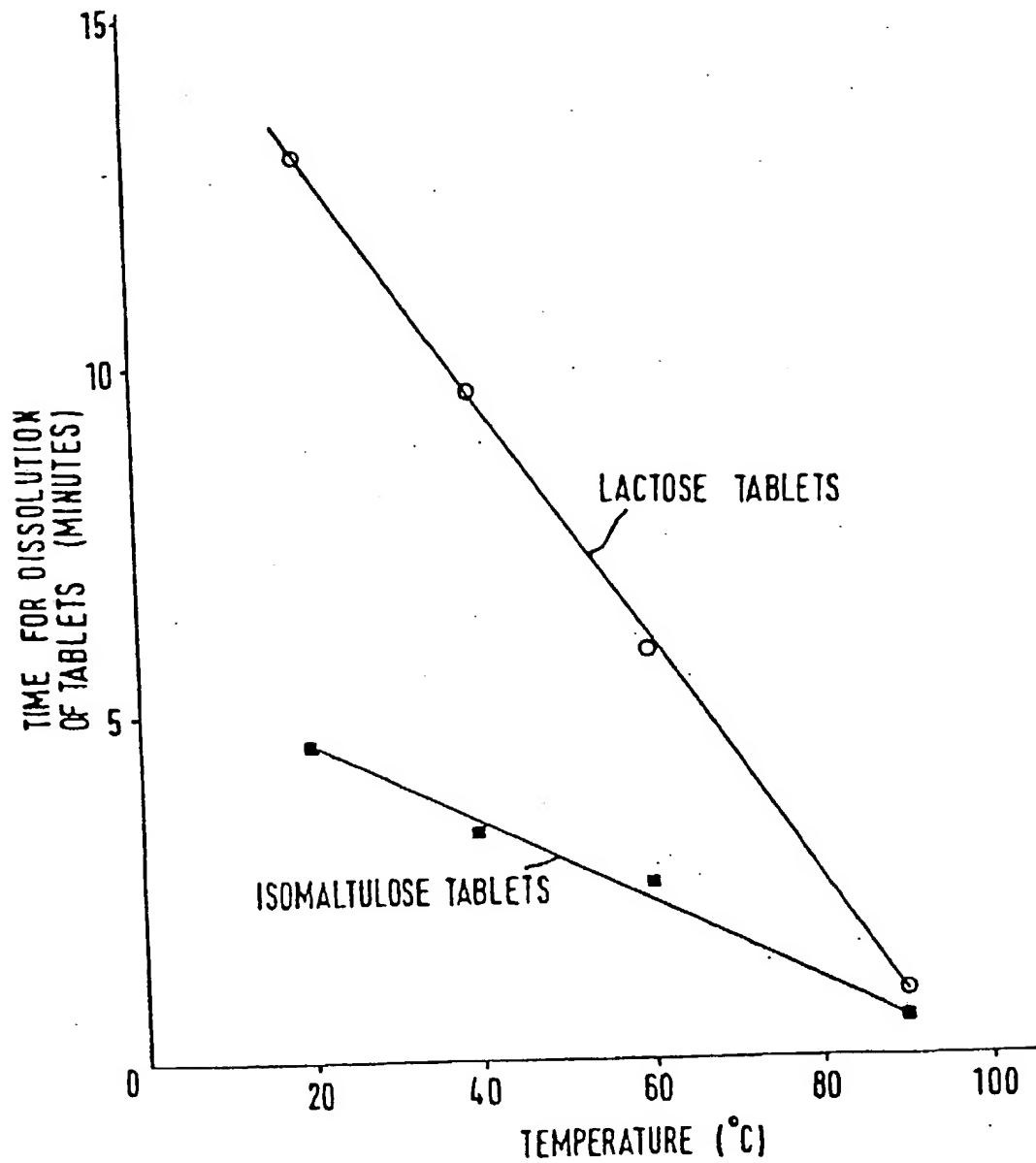
16.

ingredients and a lubricant, and the dry mix is compressed.

9. A method according to claim 8, in which an added binder is absent from the dry mix.

10. The use of isomaltulose as a diluent in tablets in total or partial replacement of lactose.

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European Patent  
Office

# EUROPEAN SEARCH REPORT

0028905

Application number

EP 80 30 3887.6

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D	<u>GB - A - 1 429 334</u> (SÜDDEUTSCHE ZUCKER-AG) * complete document * --		A 61 K 9/36 A 23 L 1/22 A 23 L 1/236
D	<u>EP - A1 - 0 001 099</u> (BAYER AG) * complete document * --		
A	<u>US - A - 3 798 054</u> (R. KAWATA et al.) * complete document * --		
A	<u>FR - A1 - 2 404 655</u> (K.K. SEIBUTSU KAGAKU KENKYUJO) * complete document * --		TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
A	<u>GB - A - 2 014 149</u> (CPC INTERNATIONAL INC.) * complete document * ----		A 23 G 3/00 A 23 L 1/00 A 23 L 2/00 A 61 K 9/00 C 12 P 19/00 C 13 K 13/00
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			δ: member of the same patent family, corresponding document
<input checked="" type="checkbox"/> The present search report has been drawn up for all claims			
Place of search Berlin		Date of completion of the search 27-01-1981	Examiner SCHULTZE